



AFRICAN MALARIA NETWORK TRUST

The First INDEPTH/MCTA/AMANET Workshop on Good Clinical Practice (GCP) for Clinical Investigators

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Workshop Report

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Introduction

The Malaria Clinical Trial Alliance (MCTA) and INDEPTH Network in collaboration with the African Malaria Network Trust (AMANET) hosted a five-day training workshop on Good Clinical Practice (GCP) for clinical trial Investigators. The Workshop took place in Bagamoyo, Tanzania on 7-11 August 2006. The 20 participants were drawn from MCTA/INDEPTH trial sites in Burkina Faso, Gabon, Ghana, Malawi, Nigeria, Senegal, and Tanzania.

The goal of the workshop was to provide knowledge on basic GCP and was arranged into five sessions (one each for the day) namely: GCP background understanding; trial preparations; conduct of the trial; and trial end. The workshop was officially opened by the Managing Trustee for AMANET, Prof. Wen L Kilama, and a keynote address given by Director of INDEPTH/MCTA, Prof. Fred Binka.

Day one: GCP background understanding

A pre-course test was undertaken in order to assess the level of GCP knowledge. The aim of the test was to assist the facilitators to identify gaps and areas requiring more emphasis.

Evolution of GCP

The first lecture for the course was on historical perspective of GCP, by Roma Chilengi. Quoting the Helsinki Declaration in his opening remark, Dr Chilengi said that even the best proven prophylactic, diagnostic, and therapeutic methods must be challenged through research for their continued effectiveness, efficiency, accessibility and quality. This was said to be one of the justifications for research on human participants. Although research on human subjects has provided substantial benefits; there have been abuses on their rights and well-being. This he said formed basis to the formation of regulatory authorities whose fundamental obligation is to safeguard human study participants by evaluating the quality, safety and efficacy of clinical studies and the data generated.

By late 1970s, many developed countries saw a proliferation of laws and regulations to guide reporting and evaluation of product data. This called for a need to rationalise and harmonise these many regulations. In 1990, representatives of the regulatory agencies and industry associations in Europe, Japan and the USA began discussions for harmonisation. Their talks gave birth to the landmark International Conference on Harmonization from which the acronym ICH is drawn. ICH forms the basis for Good Clinical Practices (GCP).

GCP is therefore defined as “an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects”. Compliance with this standard is said to provide public assurance that the rights, safety and well-being of trial participants are protected.

Investigator Responsibilities

Dr Christine Manyando addressed this topic through a subject entitled: “Who is an investigator & what does s/he do?” She began by defining an investigator as a person responsible for the conduct of the clinical trial at a trial site. The investigator is the responsible leader of the team, also called the Principal Investigator (PI). She outlined the various responsibilities the investigator categorising them into before, during, and after the study. She also gave several examples to illustrate investigator responsibilities.

Sponsor Responsibilities

On sponsorship, Dr Chilengi said that a sponsor is often a pharmaceutical company, but may also be an individual, the investigator, an institution or organization that initiates, funds, organizes and oversees the conduct of a clinical trial. Dr Chilengi also said that there are situations where an investigator may also qualify as sponsor, and in that case, s/he is defined as an individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a study participant.

Role of Regulatory Authorities

In his talk on “regulatory authorities”, Dr Nditonda Chukilizo said that a regulatory authority (RA) is a government agency or institution legally mandated to regulate a given trade or profession. This agency ensures that those being regulated comply with agreed laws, standards and norms. Regulatory authorities are responsible for ensuring that the public is protected through formulation and enforcement of regulations over medicinal products and/or conduct of clinical trials. RAs provide authorization for importation of investigational products to be used in trials, they also review product dossiers before a product can be licensed or marketed.

Role of Ethics Committees (ECs)

The role of ethics committees (ECs) was presented by Prof. Wen Kilama who said that ECs are there to represent the interest of potential research participants and the their community, to contribute to the safeguarding of their dignity, rights, safety, and well-being. The EC should ensure the observation and application of fundamental ethical principles which include: autonomy- respect of individuals by obtaining their free informed consent; justice- fair distribution of benefits and burdens of research; Beneficence and non-maleficance- the need to minimise harm while maximising benefits from the research.

Day two: Trial preparations

Day two began with a recap of the previous day. The rest of the day’s sessions then focussed on activities that build up to the initiation of the trial.

The Role DSMB

The “Role of Data Safety and Monitoring Boards” was presented by Dr Chilengi. The duty of such a body was said to be that of reviewing safety of data generated in the trial. The DSMB was said to be constituted by the sponsor before the trial begins and must have clear terms of reference and mode of operation.

GCP Compliant laboratory

This topic was given by Dr Chilengi, who began by stating that Good Laboratory Practice (GLP), like GCP, is a concept based on the Organization for Economic Corporation and Development (OECD). GLP was said to be a quality-based system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported. A GCP compliant lab was said to be one that ensures analytical test reporting, interpretation and verification are accurate and provide an audit trail to establish the reliability and integrity of studies.

Standard Operating Procedures

Dr Manyando gave this lecture stating that standard operating procedures (SOPs) are needed to ensure uniformity of performance. To be GCP compliant, all aspects of the trial must be covered by adequate SOPs. The SOPs should be simple, unambiguous and reviewed at regular intervals and regularly. She said that SOPs form the basis on which staff should be trained and re-trained on specific trial related procedures. A sample layout with content of an SOP was presented. An interactive exercise identifying the kinds of SOPs and working on its content was the task given to all participants. Participants were given opportunities to critique the SOPs they had prepared, and this stimulated a lot of discussion.

Quality Assurance and Quality Control (QA/QC)

For a study to be considered GCP compliant, Quality Assurance and Quality Control (QA/QC) must be reasonably implemented. An institutional approach to QA is very important as this requires the correct policy at the institutional level. QA was said to be “all those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements”. QC on the other hand is “the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities are fulfilled”. This session was facilitated by Dr Chilengi.

Informed Consent

It was said that the heart of GCP lies in the informed consent process. This was explained in a presentation titled “Informed Consent: Basis, importance & process” by Dr Manyando. Informed consent was said to confer on the trial the scientific credibility it needs, taken into account the well-being of the participant. It was observed that this has to be a process, and it must involve passing on appropriate information, comprehension, and voluntary decision to participate or not to participate. It was emphasized that it is important to demonstrate that the decision is made out of study participants’ own free will without any undue coercion or inducement.

The discussion on informed consent was the highlight of the second day as it generated a very lively and discussion and sharing of experience from both the participants and facilitators.

Day three: Conduct of the trial I

After having gone through the introductory and preparatory topics the previous two days, day three was another busy and exciting day going even deeper into the activities of a clinical trial. The feed back from the previous day was presented and discussed at the start on the day.

Essential Documents

The presentation on essential documents (EDs) was given by the three facilitators Drs Chilengi, Manyando and Chukilizo. The topic was broken into three parts: pre-trial, during trial and after the trial. EDs were defined as documents which individually and collectively permit the evaluation of the conduct of trial and the quality of data produced. They serve to demonstrate the compliance of the investigator, sponsor and monitor with the standard of GCP. The typical ICH investigator study file checklist was used as a guide in elaborating on the EDs.

Adverse events and their reporting

Adverse events and their reporting by Christine Manyando concluded the morning session. An adverse event was defined as any untoward medical occurrence happening after the participant has been administered study intervention. All adverse events must be reported. Serious adverse events were also defined as any adverse event that leads to hospitalization, prolongs hospitalisation, results in death, causes disability and malignancies/cancers. All serious events must be reported within the protocol specified time frames.

The study product

Dr Manyando continued to present the important topic on “handling of study product and accountability”. This session emphasised on the importance to understand requirements on handling the study product and that should be done by qualified personnel. The talk emphasized following of instructions on storage conditions, reconstitution, administration, and accountability must be followed. Training on SOPs for the product should be conducted before the product arrives at the trial site. Moreover, the sponsor and investigators need to ensure that appropriate authorisations have been obtained before importation of the study product i.e. ethical, regulatory and other agents approval where required.

Randomisation and keeping the blind

Dr Chilengi followed up with a topic on “Trial randomization and the code”. It was observed that double blind randomized controlled trial design is currently the best way to evaluate a clinical trial product. Randomisation was defined as the act of allocating study participants into treatment arms based on chance. This was said to be important in avoiding selection bias, it also ensures that potential confounding factors are evenly distributed. The code, on the other hand was said to be a listing of the actual treatment allocations. It is called the code because in blinded studies, it is concealed, only to be broken under special or inevitable circumstances and must follow prior written procedures. GCP compliance requires that the randomisation is respected, and the blind code maintained. Only after the database is locked, is when the official break of the code can be done.

After this, the class had a series of interactive sessions debating on when a clinical trial should begin, and this was followed by a role play based on hypothetical cases on sensitizing the community and on the informed consent process.

Day four: Conduct of the trial II

Role of the Clinical Monitor

Day four began with a presentation on “Role of the Clinical Monitor” by Dr William Mwatu. In this talk Dr Mwatu defined a Clinical monitor to be a qualified/trained individual in clinical trials. This person oversees the conduct of a trial, records and reports in accordance to GCP regulation as warranted by the extent and nature of protocol and complexity of the clinical trials. Overall, the monitor ensures quality control of clinical trials in respect of GCP.

Role of Data Management

The whole process of conducting clinical trials was said to involve many actors whose interactions can be complex. Dr Chilengi said that the data management unit is a critical player in clinical trials. This unit must be involved in the planning, designing and implementation of all trial related activities. The data management unit must ensure that the data being collected has passed QC. Other important roles mentioned for this unit include randomization, blinding, development of SOPs, testing the data collection procedures, internal monitoring and quality control.

The Study Coordinator

Dr. Thera began this topic by stating that this is not particularly a GCP requirement. Recently, many GCP compliant studies have succeeded because, in part, they engaged a dedicated study coordinator. The Clinical Trial Coordinator/Manager was said to be able to coordinate all activities related to clinical trials, execute some Principal Investigator (PI) role as may be designated, ensure proper documentation at all levels, development of clinical trial SOPs and supervise trial finances. Principal Investigators are typically senior and rather busy individuals with multiple responsibilities and may not always be available at the field site. The Coordinator therefore is the one who may assume responsibility and ensures that the study is adherent to GCP.

Trial Insurance

Dr Mwatu talked about “Sponsor versus investigator insurance”. Investigators and their institutions are obliged to be insured, especially against malpractice. The sponsor on the other hand is obliged to provide insurance that indemnifies the investigator/institution against trial related injuries. The insurance should also cover adequate and acceptable compensation in accordance to applicable regulatory requirements. Several examples of litigations were cited mostly from the United States. It was warned that trials in Africa are increasingly drawing international attention, and therefore must be conducted under strict GCP.

Dealing with Data Queries

In a presentation on “Dealing with data queries”, Dr Chilengi said that the intent of a query (data clarification) is to correct mistakes observed. Data queries (DQs) were said to be

generated by the data management team based on preset validation rules. DQs may be generated during the conduct of the study and at the end just before the database is locked. The Monitor ensures that all queries are appropriately resolved by the investigator and that there is correct documentation. Sample lay out of a data resolution form was presented and discussed.

Confidentiality in trials

Issues of “Confidentiality in trials” were discussed by Dr Manyando. She said confidentiality of research participant’s identity and privacy, and sponsors proprietary information is essential in fulfilment of GCP requirements. Participants were impressed upon to appreciate the need for upholding of confidentiality. Confidentiality was said to be based on the fundamental ethical principles of medical research as stated in the Helsinki Declaration.

Trial Audits

Dr Chukilizo introduced auditing as an essential activity that determines whether the clinical trial is done in accordance with GCP specifications and regulatory authorities. Auditing was said to come in many forms and could either be “routine” or “for cause” on account of suspicion of non compliance and can be retrospective. The process may be achieved through examination of essential documents, trial activities and inspection of facilities at the site. Audited reports must be communicated to sponsors but may also be made available to regulatory authorities. In appointing auditors, Dr Chukilizo said that the sponsor must take into account the qualifications and experienced of such persons for the task.

Trial termination

The last presentation discussed “Premature termination of the trial”. In this lecture, Dr Mwatu laid out circumstances under which a trial may be prematurely terminated. This he said may be initiated by the sponsor, the investigator or regulatory authorities or by the ethics committee. Investigators are obliged to inform the various parties involved on the termination, and GCP particularly requires that participants are also informed and assured of appropriate therapy and follow-up.

Iterative Activities

An exciting interactive session on adverse events was the climax of the day. Facilitators presented many case scenarios, and participants were required to identify whether these qualify as adverse events, serious adverse events or none at all.

Then the day summed up with a tour of the Bagamoyo District Hospital where participants observed activities of an on-going trial of a candidate malaria vaccine.

Day five: Trial end

Study Close Out

The last day of the workshop began with a presentation by Dr Mwatu on study close-out activities. The talk emphasized continued follow-up of adverse events and serious adverse events. Even when the trial is over, continued follow-up of pregnancies and other conditions resulting from the trial was emphasized. Other close-out activities discussed in this presentation include resolving of any data queries, the need to reconcile, return or destroy any remaining investigational products, proper keeping of study records, notification of ethics committees of the end of study and settling of financial and other issues.

Reports

Participants were then taken through the subject of reporting as presented by Dr Chilengi who said that the investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in case report forms (CRFs) and in all other required reports. The investigator should submit written summaries of the trial status to the IRB/IEC annually, or as required by the IRB/IEC. On the side of the sponsor, whether the trial is completed or prematurely terminated, the sponsor should ensure that clinical trial reports are prepared and provided to the regulatory agency (ies) as required by the applicable regulatory requirement(s). It was also said that the sponsor should also make sure that clinical study reports contributing to the product dossier meet standards of the ICH in format and content.

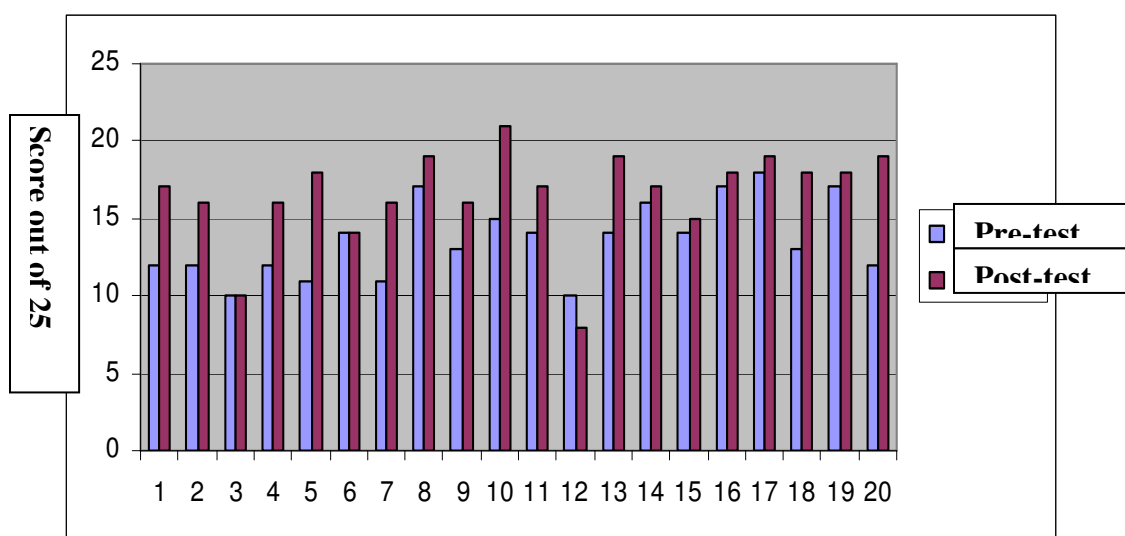
After the trial

What needs to be done when a trial is completed? This question formed the basis of the last talk titled “when a trial is completed” presented by Prof. Kilama who also gave a review of several international guidelines. Prof Kilama said that despite these guidelines, it is still not clear who takes responsibility for continued provision of improved health care, adverse events; provision of a successful intervention after the trial is over. The roles of principal investigators, researchers, sponsor, governments, donors and NGOs after the trials were also discussed.

Course Test

A post-study test was given to the participants to assess the impact and relevance of the five-day GCP course. The post-training results showed a significant gain in the mean score which we interpret as a significant increase in knowledge as shown in the results below.

Table1. Comparison of test performance



Significance test: Comparison of means

Pre-test mean	Post test mean	Gain in mean	P-value
13.6	16.55	2.95	0.0001

NB. Following on the successes of this first GCP workshop, the INDEPTH/MCTA network again in collaboration with AMANET organized a second GCP workshop on 6-11 November 2006 at the KEMRI-Wellcome Research Programme, Kilifi, Kenya. A total of 27 participants and 10 facilitators from Burkina Faso, France, Gabon, Ghana, Kenya, Malawi, Nigeria, Senegal, Tanzania, The Gambia and Uganda attended.